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| 09/060,294      | 04/15/1998  | MARTIN ROLAND JENSEN | P60953US1           | 9443             |

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400 SEVENTH STREET NW  
WASHINGTON, DC 20004

EXAMINER

ROMEO, DAVID S

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1647

DATE MAILED: 11/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/060,294

Applicant(s)

JENSEN ET AL

Examiner

David S. Romeo

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 August 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 91-97 and 133 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 91-96 is/are allowed.
- 6) ☒ Claim(s) 97 and 133 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received..
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The amendment filed 08/11/2005 has been entered. Claims 91-97 and 133 are pending. Applicant's elected group I in the paper filed 10/21/2003. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant's elected with traverse the species E/F loop substitution in the paper filed 10/21/2003. The traversal was on the ground(s) that the substitution in the E strand and in the E/F connecting loop species and the substitution in the E strand and in the E/F and D/E connecting loop species should also be examined with the elected species. This was found persuasive. The requirement was still deemed proper and was therefore made FINAL. Claims 82-84, 86, 98-103, 107-109, 111, 115, 116, 123, 125-127, 128, 130 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species or invention, there being no allowable generic or linking claim. Claims 91-97 and 133 are being examined to the extent that they read upon the elected species. Applicant timely traversed the restriction (election) requirement in the paper filed 10/21/2003.

#### ***Claim Rejections - 35 USC § 103***

Claim 133 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mouritsen (WO 95/05849) in view of {Pennica (Nature. 1984 Dec 20-1985 Jan 2;312(5996):724-9), Shirai (Nature. 1985 Feb 28-Mar 6;313(6005):803-6), or Wang (Science. 1985 Apr 12;228(4696):149-54)}, further in view of Jones (BF, cited by Applicants), and further in view of Panina-Bordignon (Eur J Immunol. 1989 Dec;19(12):2237-42) and Le (U. S. Patent No. 5,656,272).

This rejection is of record at page 3 in the Office action mailed 10/05/2004.

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Claim 97 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mouritsen (WO 95/05849) in view of {Pennica (Nature. 1984 Dec 20-1985 Jan 2;312(5996):724-9), Shirai (Nature. 1985 Feb 28-Mar 6;313(6005):803-6), or Wang (Science. 1985 Apr 12;228(4696):149-54)}, further in view of Jones (BF, cited by Applicants), and further in view of Panina-Bordignon (Eur J Immunol. 1989 Dec;19(12):2237-42) and Le (U. S. Patent No. 5,656,272) as applied to claim 133 and further in view of Hellman (WO 93/05810), Cox (WO 92/19746), and Cooke (J Exp Med. 1994 Feb 1;179(2):425-38).

Applicants argue that TNF2-1 is the human-derived equivalent of MR105. Applicants' arguments have been fully considered but they are not persuasive. The MR105 and TNF2-1 mutants are not equivalent because each comprises a different T-cell epitope inserted into a different region of TNF.

Applicants argue that the subject application does not acknowledge that TNF variants disclosed in Mouritsen provide for the induction of neutralizing antibodies. In the next sentence Applicants state that the subject application discloses that variants MR103 and MR106 provide for the induction of neutralizing antibodies. In view of the specification teaching that the antibodies induced by Mouritsen's modified TNF $\alpha$  molecules were able to interfere with TNF $\alpha$  and its receptor in vitro as well as in vivo (paragraph bridging pages 35-36), the examiner considers the latter statement to be correct. The examiner is not relying on the paragraph bridging pages 35-36 as prior art. The examiner was responding to Applicants argument that Mouritsen does not even point to any specific parts of murine TNF that would be suitable for introduction of foreign T-cell epitopes. In fact, Mouritsen teaches that substitutions in the region

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substituted in the MR103 mutant detoxify the recombinant protein (page 10, lines 14-16). In combination with Mouritsen's teaching that toxic self proteins such as TNF $\alpha$  can be simultaneously detoxified by removing or mutating biologically active protein segments (page 7, lines 11-15) and that the modified TNF $\alpha$  could be administered as an anti-TNF $\alpha$  vaccine to patients suffering from diseases where TNF $\alpha$  is important for the pathogenesis (page 14, lines 13-20, 26-30; paragraph bridging pages 14-15) teaches or suggest to one of ordinary skill in the art to produce neutralizing antibodies. The paragraph bridging pages 35-36 of the present specification confirms that Mouritsen points to specific parts of murine TNF that would be suitable for introduction of foreign T-cell epitopes.

Applicants argue that skilled artisans would only have expected that optimum variants of human TNF must resemble MR105 because MR105 is the only variant that is demonstrated to be biologically inactive. Applicants' arguments have been fully considered but they are not persuasive. Mouritsen teaches that substitutions in the region substituted in the MR103 mutant detoxify the recombinant protein (page 10, lines 14-16). The MR103 mutant is also substituted in a region not involving the B and/or G strands. Accordingly, the  $\beta$ -sheet structure of the B and G strands is preserved.

Applicants argue that one would not have been able to deduce anything from Mouritsen or Jones that points in the direction of preserving the  $\beta$ -sheet structure of the B and G strands. Applicants' arguments have been fully considered but they are not persuasive. Put another way, the limitation "preservation of the  $\beta$ -sheet structures of the B and G strands" merely limits the claim to neutralizing antibodies. Mouritsen's teaching that toxic self proteins such as TNF $\alpha$  can be simultaneously detoxified by removing or mutating biologically active protein segments (page

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7, lines 11-15) and that the modified TNF $\alpha$  could be administered as an anti-TNF $\alpha$  vaccine to patients suffering from diseases where TNF $\alpha$  is important for the pathogenesis (page 14, lines 13-20, 26-30; paragraph bridging pages 14-15) teaches or suggest to one of ordinary skill in the art to produce neutralizing antibodies.

Applicants argue that the PTO has not addressed how the skilled artisan would have expected the TNF mutants to be both non-toxic and capable of inducing neutralizing antibodies absent undue experimentation. Applicants' arguments have been fully considered but they are not persuasive. Mouritsen's teaching that toxic self proteins such as TNF $\alpha$  can be simultaneously detoxified by removing or mutating biologically active protein segments (page 7, lines 11-15) and that the modified TNF $\alpha$  could be administered as an anti-TNF $\alpha$  vaccine to patients suffering from diseases where TNF $\alpha$  is important for the pathogenesis (page 14, lines 13-20, 26-30; paragraph bridging pages 14-15) teaches or suggest to one of ordinary skill in the art to produce neutralizing antibodies from a non-toxic TNF mutant. The paragraph bridging pages 35-36 of the present specification confirms that Mouritsen's teachings are enabled.

It is not a question of whether the skilled artisan would have had to invent the subject matter of claim 97. The relevant question is whether the claimed invention would have been obvious. Mouritsen suggest the desirability, and thus the obviousness, of designing human TNF mutants that are detoxified and capable of inducing neutralizing antibodies.

Applicants argue that the language of amended claim 97 does not allow some substitution of the B and G strands. Applicants' arguments have been fully considered but they are not persuasive. Substitutions that preserve the  $\beta$ -sheet structures of the B and G strands would be

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allowed by the present claims. In other words, residues of the B and G strands could be substituted as long as the resulting structure is a  $\beta$ -sheet.

***Conclusion***

Claims 91–96 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

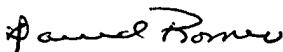
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.



DAVID ROMEO  
PRIMARY EXAMINER  
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